

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

_____	)	
WYETH,	)	
	)	
Plaintiff,	)	
	)	Civil Action No.: 06-222 JJF
v.	)	
	)	
IMPAX LABORATORIES, INC.,	)	<b>PUBLIC VERSION</b>
	)	
Defendant.	)	
_____	)	

**WYETH'S OPENING MARKMAN BRIEF**

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## I. THE NATURE AND STAGE OF PROCEEDING

Wyeth filed this patent infringement action against Impax Laboratories, Inc. (“Impax”) for its submission of an Abbreviated New Drug Application (ANDA) seeking approval to market a generic copy of Effexor<sup>®</sup> XR, Wyeth’s breakthrough drug for treating depression. Wyeth submits this Opening Markman Brief.

## II. SUMMARY OF ARGUMENT

The patents-in-suit disclose and claim methods for treating patients with depression or other disorders responsive to venlafaxine by administering “an extended release formulation” of venlafaxine hydrochloride that provides therapeutic blood plasma concentrations of the drug over 24 hours and results in less nausea and vomiting than an immediate release formulation of venlafaxine hydrochloride. The claims require either peak blood plasma levels of venlafaxine within a specified time period, or peak blood plasma levels of venlafaxine within specified concentrations. Some of the claims also require “diminished incidences of nausea and emesis.” None of the asserted method claims requires a specific extended release formulation having a specific set of inactive ingredients.

The term “extended release formulation” has a recognized meaning to those skilled in the art, **REDACTED**, that is not restricted to any particular ingredients. Consistent with that ordinary meaning, the claims themselves make clear that an “extended release formulation” is not limited to a particular set of inactive ingredients. Not only do the asserted claims not recite such limitations, but other claims (including independent product claims and dependent method claims) explicitly recite inactive ingredient limitations, indicating that the asserted method claims are not so limited. The claim interpretation asserted by Impax (which reads specific ingredients into the claim term) would render other claim terms redundant, a clear indication of a flawed construction.

The patent specification, consistent with the claims themselves, demonstrates that the term “extended release formulation” is not limited to a particular set of inactive ingredients. It broadly describes the “use aspect of the invention” (which corresponds to the asserted method

claims) in terms of pharmacokinetic properties, specifically peak blood plasma levels of venlafaxine within a specified time period or within a specified concentration. It also discloses specific preferred formulations for carrying out the disclosed methods. The specification does not, however, limit the “use aspect of the invention” to a particular formulation having a specific set of ingredients. To the contrary, the specification discloses a dissolution profile bench test that can be used to screen other formulations for practicing the invention.

**REDACTED**

The prosecution history confirms that the term “extended release formulation” is not limited to a particular set of ingredients. The patent examiner initially suggested that the broad method claims would be patentable only if the “extended release formulation” in the claims was amended to be limited to specific ingredients, showing that the examiner viewed those method claims as not limited to specific ingredients. Wyeth tentatively agreed to that amendment, but it then refiled the broad method claims without this limitation, showing that Wyeth was seeking method claims not limited to a particular formulation having a defined set of ingredients. Later in the prosecution, a second examiner objected to formulation claims that depended from one of the original broad method claims as improper dependent claims. The examiner reasoned that the method claim “does not recite any limitations describing the formulation.” Again, this shows that the patent examiners did not interpret the method claims as limited to a defined set of ingredients. The broad method claims (the asserted method claims in suit) thus issued without being limited to any specific ingredients (beyond the active ingredient, venlafaxine hydrochloride).

Extrinsic evidence also fully supports Wyeth’s construction of “extended release formulation.” Dictionaries and treatises indicate that the term “extended release formulation” is a recognized term of art not limited to a particular formulation having a specific set of ingredients. Testimony from Wyeth’s expert support the same conclusion.

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With respect to the phrase “diminished incidences of nausea and emesis” that appears in some claims, the claim language and specification suggest that “diminished incidences” means a decrease in the “frequency and/or degree” of those adverse side effects. Impax’s proposed construction, a “decrease in the number of patients suffering from nausea and vomiting,” fails to distinguish between those patients who experience mild or transitory side effects from the extended release formulation and those patients who experience more severe or long lasting side effects from an immediate release formulation. Such a construction does not comport with the plain meaning of the term, the specification, common sense, or the understanding of those skilled in the art.

Lastly, the meaning of the claim phrase “a method for eliminating the troughs and peaks of drug concentration in a patient’s blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride” is clear from the manner in which it is used in the Wyeth patents’ specification. Wyeth’s construction simply incorporates the specification’s explanation of what it means to “eliminat[e] troughs and peaks . . . .”

### **III. STATEMENT OF FACTS**

#### **A. Wyeth’s Development of Effexor XR**

In a field crowded with both innovative and generic drugs, Effexor XR has become one of the leading drugs used to treat depression, with annual U.S. sales exceeding \$2.5 billion. But behind this current success is the story of a drug of unfulfilled promise, burdened by side effects, until the patented inventions at issue here unlocked its potential.

The active ingredient in Effexor XR is venlafaxine hydrochloride. Wyeth spent years developing this drug and, in 1994, obtained FDA approval for a formulation that releases

venlafaxine soon after it is ingested.<sup>1</sup> This “immediate release” formulation is known as Effexor<sup>®</sup> and is still sold today. But Effexor, although a potent anti-depressant, suffers from two significant limitations. First, patient compliance with the dosing regimen is poor because the active ingredient is rapidly eliminated from the body, thus requiring two or three daily doses. Second, patients using Effexor often suffer adverse side effects, specifically nausea and emesis (vomiting). Consequently, many patients cannot tolerate therapeutic doses of Effexor and stop taking the drug. Indeed, the adverse side effects are so common and so severe that Effexor became known in the medical community by the pejorative nickname “Side-Effexor.” These limitations are reflected in the U.S. sales of Effexor, which plateaued at \$225 million.

Fortunately for those suffering from major depression, Wyeth’s research efforts on venlafaxine did not stop with Effexor. Long before Effexor was launched, Wyeth recognized that multiple daily dosing would not be well accepted by depressed patients and began a research effort to determine whether an extended release formulation of venlafaxine could be developed and, if so, whether it would be therapeutically effective.

The feasibility of developing a therapeutically effective extended release formulation of venlafaxine, however, was uncertain. Early work by the Wyeth inventors with hydrogel tablet technology somewhat extended the release of venlafaxine but did not succeed in sufficiently slowing the release rate of the drug in laboratory bench testing (*in vitro* dissolution testing) to meet the desired profile. Ultimately, the Wyeth inventors developed prototype formulations with slower release rates in *in vitro* laboratory tests and *in vivo* animal testing that justified the next step in development, testing in healthy volunteers. That phase of the research was extremely unpredictable.

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<sup>1</sup> For the sake of brevity only, Wyeth will use the term “venlafaxine” in this Brief to refer to both venlafaxine itself, as well as to venlafaxine hydrochloride, the salt of venlafaxine that is present in the formulation.

Even if the release of a drug is extended, one still cannot predict whether that drug will in fact be adequately absorbed to produce sufficient levels of drug in the bloodstream. In an immediate release product like Effexor, the active ingredient is released as soon as it is ingested. The drug, therefore, is available for absorption in the upper portion of the intestines, where it is most likely that the drug will be well absorbed. However, an extended release venlafaxine formulation designed for once-a-day administration must release the drug over many hours. As a result, the extended release formulation must continue to release the drug after the formulation passes into the lower intestines, including the colon. Drug absorption from the lower intestines, including the colon, is extremely unpredictable. Only through testing did Wyeth discover that venlafaxine can, in fact, be significantly absorbed in the lower intestines.

Having substantially changed the blood plasma profile compared to immediate release Effexor, it could not be assumed that Wyeth's extended release formulation would be therapeutically effective in patients. So Wyeth began a series of clinical trials to determine whether its extended release formulation of venlafaxine would be therapeutically effective. Surprisingly, not only was the extended release formulation therapeutically effective when administered once a day, but it was even *more* effective than immediate release Effexor.

This improved effectiveness was unexpected and came about because the extended release formulation was better tolerated than Effexor, particularly with respect to reducing the level of nausea and vomiting (emesis). This improvement in tolerability was extremely important. Because the therapeutic benefits of venlafaxine hydrochloride take several weeks to build after starting treatment, many patients experiencing nausea and vomiting stop taking the drug before the therapeutic benefits are experienced. Because Wyeth's extended release formulation is better tolerated than Effexor, patients are more likely to stay on the medication longer, giving the active ingredient a chance to work. And because of the better tolerability, patients also are able to take higher doses of the drug, thereby further improving its efficacy. After making these unexpected discoveries, Wyeth filed the first of its patent applications that culminated in the three patents involved in this lawsuit. The commercial embodiment of

Wyeth's research efforts, Effexor XR, which is disclosed and claimed in these patents, was subsequently approved by the FDA and launched in late 1997.

**B. The Patents-in-Suit**

The culmination of Wyeth's extensive development work is disclosed and claimed in the patents-in-suit, U.S. Patent No. 6,274,171 B1 [Ex. 1],<sup>2</sup> U.S. Patent No. 6,403,120 B1 [Ex. 2], and U.S. Patent No. 6,419,958 B2 [Ex. 3] (collectively the "Wyeth patents"). All three patents share the same patent specification. The Wyeth patents include method claims directed to once-a-day administration of extended release formulations that are therapeutically effective and achieve certain pharmacokinetic drug plasma characteristics. The patents also include product claims directed to certain formulations that will achieve those characteristics. Importantly, the Wyeth patents disclose valuable information about the dissolution profile of useful extended release formulations, thus providing a roadmap for the development of other extended release formulations that can be used to carry out the claimed methods.

In particular, Wyeth disclosed an *in vitro* dissolution profile in Table 1 that can be used as a tool to identify other extended release formulations of venlafaxine hydrochloride that are likely to meet the claimed pharmacokinetic and therapeutic properties. One of the most expensive and lengthy aspects of drug development is human testing. By using the *in vitro* test disclosed in the patents, the public can identify those formulations that are most likely to be successful in human trials, thus minimizing the risk and cost of such trials.

From the three patents-in-suit, Wyeth is asserting only claims to methods of therapy. The specific product (formulation) claims are not being asserted. From the '171 patent, method claims 20-25 are asserted. Claims 20 and 21 are representative and read as follows:

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<sup>2</sup> All exhibits cited herein are exhibits to the accompanying Declaration of Karen Jacobs Loudon.

20. A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis

which comprises administering orally to a patient in need thereof,

an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours,

said formulation containing venlafaxine hydrochloride as the active ingredient.<sup>3</sup>

21. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride

which comprises administering orally to a patient in need thereof,

an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours,

said formulation containing venlafaxine hydrochloride as the active ingredient.

From the '120 patent, method claims 1, 2, 13 and 14 are asserted. Independent claim 1 reads as follows:

A method for providing therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidence of nausea and emesis

which comprises administering orally to a patient in need thereof,

an extended release formulation that provides peak blood plasma levels of venlafaxine of no more than about 150 ng/ml,

said formulation containing venlafaxine hydrochloride as the active ingredient.

The asserted method claims of the '958 patent are virtually identical to the asserted method claims from the '171 patent except that the word "encapsulated" is not present.

The underlining highlights the three disputed claim terms that require construction: (1) extended release formulation, (2) diminished incidence of nausea and emesis, and (3) a method

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<sup>3</sup> Claims 22 and 23 of the '171 patent contain the same language as claim 20, except that the time to reach the peak blood plasma level of drug (" $T_{max}$ ") is different. Similarly, claims 24 and 25 of the '171 patent contain the same language as claim 21, except that the  $T_{max}$  is different.

for eliminating the troughs and peaks of drug concentration in a patient's blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride.

**C. The Accused Method**

Impax is seeking FDA approval for a method of treating patients with depression by administering an extended release formulation of venlafaxine hydrochloride that meets all of the claim limitations of each of the asserted claims. In an effort to avoid literal infringement, however, Impax argues that Wyeth's method claims are limited to specific formulations having a defined set of ingredients, even though the method claims, unlike Wyeth's product claims, simply recite "an extended release formulation" without being limited to specific inactive ingredients. But Impax's approach violates basic tenants of claim construction—that the claims define the invention, that unwarranted limitations should not be imported into the claims from the specification, and that claim terms should not be construed so as to render other claim limitations superfluous. And the patent specification and prosecution history confirm what the claims themselves make clear, namely, that "extended release formulation" is not restricted to specific formulations having a defined set of ingredients.

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**REDACTED**

#### **D. Prior Litigation**

The patents-in-suit have been asserted once before. In 2003, Wyeth asserted the patents against Teva Pharmaceuticals in the United States District Court for the District of New Jersey. On September 6, 2005, the Honorable William J. Martini issued a Markman ruling in which he construed several claim terms, including two of the terms at issue here. [Ex. 7]. On the eve of trial, and after summary judgment motions had been briefed and argued (but not yet decided), the parties settled the case. As part of the settlement, Teva's invalidity and unenforceability counterclaims were dismissed with prejudice, and Teva was enjoined from marketing its proposed generic product except as provided for in a license agreement that was part of the settlement. [Ex. 8]. The New Jersey district court also issued an Order in 2006 vacating its interlocutory Markman ruling. [Ex. 9].

### **IV. ARGUMENT**

#### **A. Legal Framework**

The Federal Circuit's most recent *en banc* explanation of the principles underlying claim construction is *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*). *Phillips* indicates that it reaffirms the basic principles of claim construction outlined in *Markman v. Westview Instruments, Inc.*, 52 F.3d 967 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996), *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576 (Fed. Cir. 1996), and *Innova/Pure Water, Inc. v. Safari Water Filtration Systems, Inc.*, 381 F.3d 1111 (Fed. Cir. 2004). *Phillips*, 415 F.3d at 1312. As *Phillips* explains, the starting point for any claim analysis is the "bedrock principle" that the claims define the scope of the patentee's rights. *Id.*

The words of a claim "are generally given their ordinary and customary meaning." *Id.* In some cases, that meaning "may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314. Often, however, "determining the ordinary and customary

meaning requires examination of terms that have a particular meaning in a field of art.” *Id.* In such cases, the court must look to “those sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean.” *Id.* Those sources include “the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art.” *Id.*

The claims themselves “provide substantial guidance as to the meaning of particular claim terms.” *Id.* The context in which a term is used in an asserted claim “can be highly instructive.” *Id.* For example, as explained in *Phillips*, the claim term “steel baffles” strongly implies that the term “baffles” does not inherently require objects made of steel. *Id.* Other claims “can also be valuable sources of enlightenment.” *Id.* Because claim terms are normally used consistently throughout the patent, “usage of a term in one claim can often illuminate the meaning of the same term in other claims.” *Id.* Differences among claims “can also be a useful guide in understanding the meaning of particular claim terms.” *Id.* For example, “the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim.” *Id.* at 1314-15.

How a person of ordinary skill in the art understands a claim term “provides an objective baseline from which to begin claim interpretation.” *Id.* at 1313. It is also “always necessary to review the specification to determine whether the inventor has used any terms in a manner inconsistent with their ordinary meaning.” *Vitronics*, 90 F.3d at 1582. Consequently, the patent’s specification is “the single best guide to the meaning of a disputed term.” *Phillips*, 415 F.3d at 1315. For example, the specification “may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess.” *Id.* at 1316. But as *Vitronics* states, “a patentee may choose to be his own lexicographer and use terms in a manner other than their ordinary meaning, as long as the special definition of the term is *clearly stated* in the patent specification or file history.” 90 F.3d at 1582 (emphasis added). The specification may also “reveal an intentional disclaimer, or disavowal, of claim scope by the

inventor.” *Phillips*, 415 F.3d at 1316. But as *Innova* states, such a disavowal of claim scope must be “*clear and unmistakable*.” 381 F.3d at 1120 (emphasis added). And *Phillips* itself cautions against “the danger of reading limitations from the specification into the claim.” 415 F.3d at 1323. In addition, *Phillips* “expressly reject[s] the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment.” *Id.*

The prosecution history also is “intrinsic evidence” that should be considered whenever claim terms are construed. *Id.* at 1317. The prosecution history “provides evidence of how the PTO and the inventor understood the patent.” *Id.* But “because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes.” *Id.* Nonetheless, “the prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be.” *Id.*

Extrinsic evidence—including dictionaries, learned treatises, and inventor and expert testimony—may be considered in claim construction, but it is less significant than the intrinsic record in determining the legally operative meaning of the claim language. *Id.* Dictionaries and treatises can have a role in determining the ordinary and customary meaning of terms because “[a] dictionary definition has the value of being an unbiased source ‘accessible to the public in advance of litigation.’” *Id.* at 1322. Expert testimony “can be useful to a court for a variety of purposes, such as to provide background on the technology at issue, to explain how an invention works, to ensure that the court’s understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field.” *Id.* at 1318.

**B. Construction of “Extended Release Formulation”**

The parties dispute the meaning of the term “extended release formulation.” Wyeth contends that the term means:

a formulation, other than a hydrogel tablet, which releases the active ingredient at a slower rate than the immediate release formulation of the active ingredient such that the dosing frequency is once-a-day rather than the plural daily dosing for the immediate release formulation.

Impax contends that the term means:

a formulation comprising venlafaxine, microcrystalline cellulose, and, optionally, HPMC coated with a mixture of ethyl cellulose and HPMC in an amount needed to provide a specific unit dosage administered once-a-day to provide a therapeutic blood plasma level of venlafaxine over the entire 24-hour period of administration.

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Similarly, a leading pharmaceutical textbook (Remington: The Science and Practice of Pharmacy) defines extended release formulations as follows:

**Extended-release dosage forms** (popularly known as timed-release or sustained-release) are defined as those that allow at least a twofold reduction in dosing frequency as compared to the drug presented in a conventional form, eg, a solution or a prompt drug-releasing conventional solid dosage form.

[Ex. 4 at ¶ 7 and Ex. 4 at Ex. B at 598].

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In addition, Wyeth's expert in the fields of the development and evaluation of pharmaceutical dosage forms, Dr. James McGinity, confirms what is clear from the above-identified evidence, that the ordinary and customary meaning of extended release formulation does not include any specific set of ingredients. [Ex. 4, McGinity Decl. at ¶¶ 7-11].

Thus, the only issue as to interpreting the term "extended release formulation" is whether the intrinsic record (claims, specification, and prosecution history) "clear[ly] and unmistakabl[y]" demonstrates that the patentees defined the term to mean something other than its ordinary meaning and limited the term to mean specific formulations with a defined set of ingredients. *Innova*, 381 F.3d at 1120. As this Court stated in *Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 405 F. Supp. 2d 495, 502 (D. Del. 2005), *aff'd in relevant part*, 457 F.3d 1284 (Fed. Cir. 2006), "a court should . . . interpret the language in a claim by applying the ordinary and accustomed meaning of the words in the claim . . . . If the patent inventor clearly supplies a different meaning; however, then the claim should be interpreted according to the meaning supplied by the inventor." *See also Markman*, 52 F.3d at 980 (Although a patentee is free to be his own lexicographer, any special definitions given to words must be clearly set forth in the patent).

As demonstrated below, the intrinsic record does not support jettisoning the ordinary and accustomed meaning of "extended release formulation" in favor of an artificial definition that

requires specific ingredients. The claims, the specification, and the prosecution history clearly demonstrate that the term “extended release formulation” is used in the patents consistent with its ordinary and accustomed meaning. The specification, at most, reflects that the inventors were not successful in achieving their desired release rate with their existing hydrogel tablet technology. Wyeth’s construction takes into account these statements, and excludes hydrogel tablets from what is otherwise the ordinary and accustomed meaning of “extended release formulation.”

### 1. The Claim Language

Three features of the claims indicate that Wyeth used “extended release formulation” in accordance with its ordinary meaning.

First, the asserted method claims recite “extended release formulation” without specifying any inactive ingredients, whereas other (unasserted) claims recite “extended release formulation” and specify inactive ingredients. Claim 1 of the ‘171 patent is representative of the latter and reads:

An extended release formulation of venlafaxine hydrochloride comprising a pharmaceutically acceptable capsule containing spheroids comprised of from about 6% to about 40% venlafaxine hydrochloride by weight, about 50% to about 94% microcrystalline cellulose, NF, by weight, and optionally from about 0.25% to about 1% by weight of HPMC, USP, wherein the spheroids are coated with a film coating composition comprised of ethyl cellulose and HPMC.<sup>4</sup>

In contrast, claim 20 of the ‘171 patent is representative of the asserted method claims and reads:

A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis

which comprises administering orally to a patient in need thereof,

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<sup>4</sup> HPMC is an abbreviation for hydroxypropylmethylcellulose.

an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours,

said formulation containing venlafaxine hydrochloride as the active ingredient.

As a matter of common usage, one skilled in the art would understand that these claims differ in scope—with specific inactive ingredients recited when the claims are limited to specific formulations with those ingredients, and with no specific ingredients recited when the claims are not so limited.

This Court addressed a similar situation in *Pfizer*. In that case, the issue was whether claim 1 was limited to a racemic mixture, which was identified in the patent by the “±” designation. Claim 1 did not have such a designation, but dependent claim 5 did. In holding that claim 1 was not limited to a racemic mixture the Court stated:

Further, that the “±” designation was used in the express language of claim 5 and not in the language of the other claims suggests to the Court that the inventor knew how to limit a claim to a racemate, but chose not to so restrict the other claims of the patent.

*Pfizer*, 405 F. Supp. 2d at 504 (citations omitted).<sup>5</sup> By the same token, the inventors here knew how to limit a claim to extended release formulations that required specific inactive ingredients. They did so with independent claim 1. They did not do so for the method claims, clearly indicating that the method claims have no such formulation ingredient restrictions.

Second, every asserted claim not only includes a limitation reciting the term “extended release formulation,” but also includes the following limitation: “said formulation containing venlafaxine hydrochloride as the active ingredient.” Claim 20 of the ‘171 patent is again representative:

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<sup>5</sup> Likewise, in *Phillips*, in concluding that the meaning of “baffles” in independent claim 1 did not include the ability to perform a certain function, the Court looked to independent claim 17 that used the same term “baffles,” but that also had a specific limitation that required the “baffles” to perform the function in question. 415 F.3d at 1324-25. According to the Court, the additional limitation in claim 17 “would be unnecessary if persons of skill in the art understood that the baffles inherently served such a function.” *Id.*

A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis

which comprises administering orally to a patient in need thereof,

an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours,

said formulation containing venlafaxine hydrochloride as the active ingredient.

By specifically identifying one ingredient of the “extended release formulation,” namely, venlafaxine hydrochloride, the patent claims convey to those skilled in the art that the formulation itself is not limited to any other specific ingredient. Just as the claim term “steel baffles” in *Phillips* “strongly implies that the term ‘baffles’ does not inherently mean objects made of steel,” 415 F.3d at 1314, in this case, “said [extended release] formulation containing venlafaxine hydrochloride . . .” strongly implies that the term “extended release formulation” does not inherently mean a formulation that contains venlafaxine hydrochloride, or any other specific ingredient. Thus, Impax’s claim construction, which seeks to define “extended release formulation” as requiring a litany of ingredients, “flies into the sun that is the plain import of the claim language . . . .” *Innova*, 381 F.3d at 1122.

Third, some of the asserted method claims include dependent claims that recite specific ingredients for the extended release formulations used in the method. For example, independent claim 1 of the ’120 patent recites a method comprised of administering “an extended release formulation,” without specifying the ingredients other than venlafaxine hydrochloride. [Ex. 2]. Dependent claim 3 of the ’120 patent, however, further limits claim 1 by specifying an extended release formulation with specific inactive ingredients:

The method of claim 1 wherein the extended release formulation comprises venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and optionally, HPMC.

If, as Impax suggests, the term “extended release formulation” of claim 1 requires a formulation that includes “venlafaxine, microcrystalline cellulose and optionally HPMC,” these limitations in claim 3 of the ’120 patent would be superfluous, and the doctrine of claim differentiation would

be violated. The Federal Circuit has repeatedly rejected claim constructions that produce such a result.

For example, in *Phillips* the issue was whether language in independent claim 1 of the patent calling for “steel baffles extending inwardly from the steel shell walls” required that the baffles extend from the walls at an angle, *i.e.*, not at 90°. In reversing a lower court ruling that required such a limitation, the Court pointed to language in dependent claim 2 that called for the “baffles” to be “disposed at angles for deflecting projectiles such as bullets . . . .” *Phillips*, 415 F.3d at 1324. According to the Court, “[t]he inclusion of such a specific limitation on the term ‘baffles’ in claim 2 makes it likely that the patentee did not contemplate that the term ‘baffles’ already contained that limitation.” *Id.*; *see also Abbott Labs. v. Andrx Pharms., Inc.*, 473 F.3d 1196, 1209 (Fed. Cir. 2007) (“the language of the claims and claim differentiation imply that the ‘pharmaceutically acceptable polymer’ term in claim 1 is likely broader than the ‘hydrophilic water-soluble polymer’ described in [dependent] claim 2 and encompasses more compounds than those listed in [dependent] claim 3”). Impax’s proposed definition violates these principles of claim construction.

In the vacated Markman ruling from the Teva case, Judge Martini acknowledged that “[b]ecause claim 3 [quoted above] includes the additional limitation of specific ingredients, the Court agrees with Wyeth that a presumption arises that claim 1 [quoted above] does not include that limitation,” and that “the plain language of the claims implies that ‘extended release formulation’ does not include specific ingredients.” [Ex. 7 at 7]. Wyeth respectfully submits that Judge Martini erred, however, in not following these basic principles of claim construction and concluding that the patent specification mandated a different result. As discussed below, it does not.

Thus, the claims themselves compel a claim construction that does not limit the term “extended release formulation” to specific ingredients.

## 2. The Patent Specification

Consistent with the asserted method claims, the patent specification describes the inventions broadly. For example, the Abstract reads:

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, an antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets. More particularly, the invention comprises an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, HPMC coated with a mixture of ethyl cellulose and HPMC.

[Ex. 1, Abstract].<sup>6</sup> The first sentence describes the broad invention—extended release formulations of venlafaxine that control blood plasma levels of the drug and reduce the nausea and vomiting as compared to the immediate release formulation—without mentioning a specific set of ingredients. The second sentence, introduced with the narrowing phrase “more particularly,” describes a subset of the first sentence and lists the ingredients in a specific extended release formulation that can be used to carry out the broadly described invention.

Likewise, the specification describes a broad “use aspect of this invention,” which corresponds to the method claims asserted by Wyeth, as follows:

[I]n accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

[Ex. 1, col. 2:38-45 (emphasis added)]. Nothing in this statement suggests that “moderating the plural blood plasma peaks” is dependent on a specific extended release formulation having a

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<sup>6</sup> The three patents-in-suit have the same specification, with the exception of the first paragraph providing the lineage of parent patent applications. As a result, citations will only be provided for the '171 patent.

defined set of ingredients. The specification also describes “the use aspect of the invention” as follows:

Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

[Ex. 1, col. 2:55-62 (emphasis added)]. Here again, nothing in this statement suggests that “reducing the level of nausea and incidence of emesis” is dependent on a specific extended release formulation having a defined set of ingredients.

At various points, the specification also describes the extended release formulations of the invention in terms of their pharmacokinetic properties and by contrasting the properties of extended release and immediate release formulations. The specification describes immediate release formulations as follows:

Venlafaxine hydrochloride is presently administered to adults . . . in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until subtherapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug.

[Ex. 1, col. 1:63-col. 2:7]. In contrast, the specification then describes extended release formulations as follows:

In accordance with this invention, there is provided an extended release (ER), encapsulated formulation containing venlafaxine hydrochloride as the active drug s [sic] component, which provides in a single dose, a therapeutic blood serum level over a twenty four hour period.

[Ex. 1, col. 2:15-19 (emphasis added)]. The specification further contrasts the blood plasma profiles resulting from the immediate release and extended release dosage forms:

In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine Is [sic] hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours

(optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours.

[Ex. 1, col. 2:24-38 (emphasis added)].

The specification's comparison of the immediate release and extended release formulations of venlafaxine hydrochloride in terms of drug release rate and dosing frequency is fully consistent with the ordinary and customary meaning of the term "extended release formulation."

Further, the specification discloses a screening tool useful in selecting extended release formulations that could be used in practicing the claimed invention:

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form.

[Ex. 1 at col. 6:42-45]. Here again, the specification describes the extended release formulations that can be used in the invention in terms of pharmacologic properties ("twenty-four hour therapeutic blood levels"), not in terms of specific ingredients.

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Elsewhere, the specification uses the term "extended release formulation" in describing prior art. For example, the specification states that "[e]xtended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology." [Ex. 1, col. 1:13-15]. Since claim terms are "normally used consistently throughout the patent," *Phillips*, 415 F.3d at 1314, Impax's construction of "extended release formulation" as being limited to specific ingredients violates this rule as well.

Impax focuses exclusively on certain specific extended release formulations described in the specification for carrying out Wyeth's invention, and imports those limitations (in this case specific inactive ingredients) into the claims. Even when a specification describes only a single

embodiment of the invention, however, the Federal Circuit has “expressly rejected the contention” that the claims should be construed as limited to that embodiment. *Phillips*, 415 F.3d at 1323.

In *Phillips* itself, the Court refused to limit the scope of the term “baffles” to acute or obtuse angle configurations, notwithstanding that all of the examples were so limited. *Id.* at 1329 (Lourie, J., concurring in part and dissenting in part). Indeed, the Court recognized that “persons of ordinary skill in the art rarely would confine their definitions of terms to the exact representations depicted in the embodiments.” *Id.* at 1323. Thus, contrary to Impax’s approach, limitations should not be imported from specification embodiments into claims. *See also Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1290 (Fed. Cir. 2006) (“while the examples do describe reaction sequences that produce racemates, restricting claim 1 on this basis would improperly import limitations from the specification into the claims . . . .”); *Ventana Med. Sys., Inc. v. Biogenex Labs., Inc.*, 473 F.3d 1173, 1181-82 (Fed. Cir. 2006) (The fact that all disclosed embodiments employed “direct dispensing” did not justify limiting the claimed “dispensing” step to “direct dispensing”); *Innova*, 381 F.3d at 1122 (“the law does not require the court, where an applicant describes only a single embodiment, to construe the claims as limited to that one embodiment . . . . Indeed, such a construction is not encouraged or presumed.”) (citations omitted).

Impax, like Judge Martini [Ex. 7 at 8-9], focuses on the following two portions of the specification to suggest that Wyeth “acted as its own lexicographer” and defined “extended release formulation”:

The formulations of this invention comprise an extended release formulation of venlafaxine hydrochloride comprising a therapeutically effective amount of venlafaxine hydrochloride in spheroids comprised of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, HPMC coated with a mixture of ethyl cellulose and HPMC.

[Ex. 1, col. 2:63-3:2]. And:

The extended release formulations of this invention are comprised of 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl]cyclohexanol hydrochloride in admixture with microcrystalline cellulose and HPMC.

Formed as beads or spheroids, the drug containing formulation is coated with a mixture of ethyl cellulose and HPMC to provide the desired level of coating, generally from about two to about twelve percent on a weight/weight basis of final product or more preferably from about five to about ten percent (w/w), with best results obtained at from about 6 to about 8 percent (w/w).

[Ex. 1, col. 4:9-19].

Impax, however, has not adopted this characterization of the “formulations of this invention” wholesale into its definition of “extended release formulation.” For example, Impax’s proposed construction requires “venlafaxine” not “venlafaxine hydrochloride”—the specific water-soluble pharmaceutical salt of venlafaxine recited in the specification. In addition, Impax’s proposed construction does not refer to “spheroids.” Impax’s picking and choosing from these paragraphs is itself evidence that Impax’s proposed construction is flawed, and that these paragraphs do not constitute “lexicography.” As *Phillips* recognized, “if we once begin to include elements not mentioned in the claim, in order to limit such a claim . . . , we should never know where to stop.” 415 F.3d at 1312 (quoting *McCarty v. Lehigh Valley R.R. Co.*, 160 U.S. 110, 116 (1895)).

In any event, these specification statements do not represent a “special definition of the term [that] is clearly stated” in a manner that would require jettisoning the ordinary and accustomed meaning of “extended release formulation,” particularly when considered in light of the entire intrinsic record. See *Vitronics*, 90 F.3d at 1582,

These passages use the phrase “the formulations of this invention.” Judge Martini concluded that this phrase circumscribes what Wyeth invented and signals that Wyeth was acting as its own lexicographer and defined the term “extended release formulation” to require the ingredients listed thereafter. [Ex. 7 at 8-9]. But a careful reading of the entire specification, in combination with the claims, demonstrates that the phrase “the formulations of this invention” merely reflects that the specification discloses first the “use” and later the “formulation” inventions. The phrase does not signal lexicography, does not limit the formulation invention, and most certainly does not limit the “method of use claims.” See *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1325-26 (Fed. Cir. 2003)(patent specification referring to the

invention as “uniquely characterized” by being the product of exogenous DNA does not justify importing the “exogenous” limitation into the asserted claims because “the asserted claims do not contain such an express limitation”); *Golight, Inc. v. Wal-Mart Stores, Inc.*, 355 F.3d 1327, 1331-32 (Fed. Cir. 2004)(patent specification statement that the “apparatus in accordance with the present invention includes” certain features does not justify limiting claims to those features because “we have outright rejected the notion that disclosure of a single embodiment necessarily limits the claims”).

To the contrary, the “use aspect of the invention” is described entirely in terms of therapeutic and pharmacokinetic results achieved — not a specific extended release formulation having a defined set of ingredients. The “use aspect of the invention” is based upon the discoveries that extended release dosage forms of venlafaxine hydrochloride having the claimed pharmacokinetic properties are feasible, therapeutic, and provide a reduction in the incidence of nausea and emesis. The “formulations of this invention” in contrast merely embody certain specific extended release formulations that Wyeth developed that are capable of achieving the desired drug level profiles. These formulations were explicitly claimed in the product claims (*e.g.*, claim 1 of the ’171 patent). But they are only examples of the formulations that might work in “the use aspect of the invention.” The method claims, in contrast, were drafted to only require “an extended release formulation” that achieves defined pharmacokinetic and therapeutic results without reciting a specific formulation having a defined set of ingredients.

Lastly, the specification describes the inventors’ attempts to use hydrogel tablet technology as follows:

Numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies.

[Ex. 1, col. 40:60-64]. And:

Thus, the desired dissolution rates of sustained release dosage forms of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the film-coated spheroid compositions of this invention.

[Ex. 1, col. 10; ll. 53-57]. Judge Martini concluded that these statements disclaimed hydrogel tablets, and therefore Wyeth's ordinary meaning construction of "extended release formulation" could not apply because the claims could not cover that which was disclaimed. [Ex. 7 at 10]. Those statements, however, say nothing about extended release formulations of venlafaxine hydrochloride like the one adopted by Impax (which is not a hydrogel tablet), and cannot justify excluding such formulations from Wyeth's method claims. Statements of disavowal or disclaimer must be clear and unequivocal and should be narrowly construed. *See, e.g., Micro Chem., Inc. v. Great Plains Chem. Co.*, 194 F.3d 1250, 1260-61 (Fed. Cir. 1999) (Patentee's statements about the failure of the prior art Brewster machine (which employed a "weight dump method") were not a disclaimer of the "weight dump method in general."). Moreover, to insure that Wyeth's proposed claim construction reflects the specification's statements regarding "hydrogel tablets," Wyeth's proposed claim construction explicitly excludes hydrogel tablets from what is otherwise a construction that is consistent with the ordinary meaning of "extended release formulation."

### **3. The Prosecution History**

Three events in the prosecution history provide unambiguous evidence of how the Patent Office understood the term "extended release formulation."

First, the examiner viewed the "extended release formulation" recited in the method claims as broader than the specific formulations recited in the product claims. Specifically, in the application filed March 20, 1997, the claims included product claims that specified the ingredients in extended release formulations and method claims that recited the term "extended release formulation" without reciting any inactive ingredients. [Ex. 11 at WYETH 002-000793-806]. The independent product claim 1 read as follows:

An encapsulated, extended release formulation of venlafaxine hydrochloride comprising

a hard gelatin capsule containing a therapeutically effective amount of spheroids comprised of

venlafaxine hydrochloride, microcrystalline cellulose and HPMC coated with ethyl cellulose and HPMC.

[Ex. 11 at WYETH 002-000804]. Claim 9, which is representative of the two submitted method claims (claims 9 and 10), and which is identical to claim 20 of the '171 patent, reads:

A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis

which comprises administering orally to a patient in need thereof,

an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours,

said formulation containing venlafaxine hydrochloride as the active ingredient.

[Ex. 11, at WYETH 002-000805].<sup>7</sup> The examiner suggested that the product claims, but not the method claims, were patentable over the prior art. [Ex. 11 at WYETH 002-000850-852]. The examiner also suggested that the method claims would be patentable if they were amended so that they depended from the product claims. [*Id.* at WYETH 002-000850]. By doing this, the method claims would have been limited to methods using extended release formulations having the specific inactive ingredients recited in the product claims. In other words, the examiner viewed the method claims as broader than the product claims and did not understand the term "extended release formulation" in the method claims to mean a specific extended release formulation with a specific set of ingredients. This is compelling evidence, in and of itself, as to how one of skill in the art would view the term "extended release formulation" as used in the method claims.

Second, Wyeth initially agreed to the examiner's suggestion to make the method claims dependent upon the product claims. The examiner made an examiner's amendment to this effect and further noted that if the amendment was not acceptable, the applicant should file an

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<sup>7</sup> Original application claim 10 is identical to claim 21 of the '171 patent, except for the inadvertent omission of the term "venlafaxine hydrochloride" in line 2 of claim 10. That term correctly appears in patent claim 21.

amendment. [Ex. 11 at WYETH at 002-000854]. Thereafter Wyeth reconsidered but, instead of filing an amendment, Wyeth abandoned the application and filed a continuation-in-part application. [Ex. 11 at WYETH 002-000911 and Ex. 12 at WYETH 002-000564-583]. In the continuation-in-part application, Wyeth refiled its original independent method claims 9 and 10 as new independent method claims 13 and 14, reciting “an extended release formulation” without any limitation to a specific set of ingredients or making them dependent on claims that contained a specific set of ingredients. [Ex. 12 at WYETH 002-000582]. In other words, Wyeth recognized that the “extended release formulation” of its method invention is not limited to a specific extended release formulation having a defined set of inactive ingredients, and it chose to pursue method claims without that limitation.

Third, the examiner expressly stated that the method claims “[d]o not recite any limitations describing the formulation.” In the continuation-in-part application, Wyeth added product claims (claims 17 and 18) that depended upon independent method claim 14 and that recited specific ingredients of the extended release formulation. [Ex. 12 at WYETH 002-000583]. Those claims read as follows:

14. A method for eliminating the troughs and peaks of drug concentration in a patients blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride

which comprises administering orally to a patient in need thereof,

an encapsulated, extended release formulation that provides a peak blood plasma level of venlafaxine in from about four to about eight hours,

said formulation containing venlafaxine hydrochloride as the active ingredient.

17. An extended release formulation according to claim 14 wherein the spheroids are composed of about 8.25% by weight of venlafaxine hydrochloride and about 91.75% by weight of microcrystalline cellulose, with a coating of from 3 to 5 % by weight of the total weight.

18. An extended release formulation according to claim 14 wherein the spheroids are composed of about 16.5% by weight of venlafaxine hydrochloride and about 83.5% by weight of microcrystalline cellulose, with a coating of from 4 to 6 % by weight of the total weight.

[Ex. 12 at WYETH 002-000582-583]. The examiner objected to claims 17 and 18 on the following grounds:

Claims 17 and 18 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The formulation of claims 17 and 18 improperly depends on claim 14 a method since claim 14 does not recite any limitations describing the formulation.

[Ex. 12 at WYETH 002-000718 (emphasis added)]. Thus, the examiner understood that the term “extended release formulation” in the method claims as “not recit[ing] any limitations describing the formulation.”

Judge Martini concluded that this prosecution history “adds, at most, nothing more than the claims themselves reveal.” [Ex. 7 at 12]. Wyeth respectfully disagrees. To the contrary, the prosecution history conclusively establishes that both Wyeth and the examiner fully recognized that the method claims are not limited to specific inactive ingredients. While the specification is no doubt important in construing claim terms, so too is the prosecution history. As *Phillips* stated, “[l]ike the specification, the prosecution history provides evidence of how the PTO and the inventor understood the patent.” 415 F.3d at 1317 (citation omitted). And if this prosecution history says anything, it is that the PTO and Wyeth understood that the term “extended release formulation” in the method claims is not limited to a specific set of inactive ingredients.

#### 4. Extrinsic Evidence

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Effexor XR, which is disclosed as a preferred embodiment in Wyeth’s patents, consists of spheroids contained in a capsule. The spheroids of the preferred embodiment are composed of a core containing the active ingredient and an extended release coating containing ethylcellulose and HPMC. When the capsule is ingested, the capsule dissolves and the active ingredient slowly

diffuses through the coating of the spheroids. Using different total amounts of coating and different ratios of ethylcellulose and HPMC, the rate of release of the active ingredient is extended and a diffusion profile consistent with Table 1 of the patents can be achieved.

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**REDACTED**

Extrinsic evidence on the ordinary and customary meaning of “extended release formulation,” and how one skilled in the art would understand the use of that term in Wyeth’s

patents, is also presented in the expert declaration of Dr. McGinity. [Ex. 4]. Dr. McGinity is an expert in the field of the development and evaluation of pharmaceutical dosage forms. Based on his expertise and review of the intrinsic record, Dr. McGinity believes that the only modification to the ordinary and customary meaning of “extended release formulation” conveyed by Wyeth’s patents is the exclusion of hydrogel tablets. [Ex. 4 at ¶¶ 26-34].

In summary, the language of the claims themselves, the specification, the prosecution history, : **REDACTED** established pharmaceutical treatises, and the expert opinion of Dr. McGinity all lead to the same conclusion: the term “extended release formulation” should be construed broadly, as Wyeth proposes, without limitation to a defined set of inactive ingredients.

### **C. Construction Of “Diminished Incidences Of Nausea And Emesis”**

The parties dispute the meaning of the phrase “diminished incidences of nausea and emesis.” Wyeth contends that the phrase means:

the degree and/or frequency of nausea and emesis from the extended release formulation administered once-a-day is less than what would be experienced by patients receiving the same total daily dose of an immediate release formulation that is administered at least twice a day.

Impax contends that the phrase means:

a decrease in the number of patients suffering from nausea and vomiting compared to patients receiving the same total daily dose of an immediate release formulation that is administered at least twice a day.

The claim language, patent specification, prosecution history, and extrinsic evidence mandate the construction proposed by Wyeth.

#### **1. The Claim Language**

The claim language itself, read in the context of the claims in which it appears, demonstrates that “diminished incidences” means a reduction in the “degree and/or frequency” of nausea and vomiting, as Wyeth proposes, not just “a decrease in the number of patients” suffering from nausea and vomiting. Claim 20 of the ’171 patent is representative and reads:

A method for providing a therapeutic blood plasma concentration of venlafaxine over a twenty four hour period with diminished incidences of nausea and emesis

which comprises administering orally to a patient in need thereof,

an encapsulated, extended release formulation that provides a peak plasma level of venlafaxine in from about four to about eight hours,

said formulation containing venlafaxine hydrochloride as the active ingredient.

[Ex. 1].

The claim language itself is consistent only with Wyeth's proposed construction. The claims use the word "diminished." This word is not used in the specification. The specification describes "a lower incidence of nausea and vomiting" and a "reduce[d] . . . level of nausea and incidence of emesis." Since "diminish" means "to make less or cause to appear less: to reduce in size, *number or degree*" [Ex. 16 at 634 (emphasis added)], the use of the phrase "diminished incidences" in the claims is consistent with a reduction in the "degree and/or frequency of nausea and vomiting." On the other hand, if the benefit with respect to nausea and vomiting was meant to be assessed solely by "a decrease in the number of patients suffering from nausea and vomiting," as Impax argues, "diminished" is an odd choice of words to express such a restricted concept -- one would have expected instead the use of a word that is restricted to "a decrease in *number*" such as "fewer."

## 2. The Patent Specification

The adverse side effects of nausea and vomiting are discussed in the specification three times. First, the Abstract discloses that the invention "provides a lower incidence of nausea and vomiting than conventional tablets." [Ex. 1, Abstract]. Second, in the "Background of the Invention," the specification describes side effects associated with conventional tablets:

Venlafaxine hydrochloride is presently administered to adults in compressed tablet form . . . in divided doses two or three times a day. . . . With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

[Ex. 1, col. 11, 63 - col. 2, 1. 11]. And third, in the “Brief Description of the Invention,” the specification describes clinical advantages of the invention as follows:

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week and one 12-week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride . . . .

[Ex. 1, col. 2, 11. 46-62].

Among the improvements concerning nausea described in the Brief Description of the Invention is a reduction by adaptation in the level of nausea after initial administration. The reference to “adaptation” means that patients adapt to the medication (*i.e.*, initial side effects become less severe or disappear over time). Thus, this example of one of the types of improvement in nausea and emesis described in the specification does not require the complete absence of nausea or emesis during the course of treatment, but includes a reduction in those side effects after initial administration. This improvement is consistent with Wyeth’s construction of “diminished incidences of nausea and emesis” (a reduction in the “degree and/or frequency of nausea and emesis”) because it includes this measure of improvement, among other measurements. This improvement is not consistent with Impax’s construction (“a decrease in the number of patients suffering from nausea and vomiting”). Indeed, Impax’s construction fails to take into account the duration and/or severity of nausea and vomiting over time, a measure of adaptation to the medication. Plainly, the specification contemplates that such improvements fall within the scope of the benefits achieved by the invention.

It is also significant that the Abstract describes the improvement in side effects achieved by the invention as “a lower incidence of nausea and vomiting” and the Brief Description of the Invention refers to the improvement as “reducing the level of nausea and incidence of emesis.” In other words, the patents describe the improvement in nausea as both a “lower incidence” of

nausea and a “reduced level” of nausea, thus treating incidence and level interchangeably. And the term “level” certainly embraces both degree and frequency. For example, Random House Webster’s College Dictionary defines level as “an extent, measure, or degree of intensity, concentration, quantity, etc.” [Ex. 21 at p. 763 (13.)]

The vacated Markman ruling cites to the passage in the specification discussing the number of patients experiencing nausea with the conventional immediate release formulation, and concludes that it demonstrates that the “patentees were concerned with the number of patients experiencing side effects, not necessarily the severity of those side effects.” [Ex. 7 at 17]. This argument is flawed for several reasons.

First, the word “incidence” is not used in the discussion in the Background of the Invention that addresses the problems associated with the conventional immediate release formulation. Moreover, nowhere in the specification are “percentage” and “incidence” equated. Second, the claims could have defined the invention solely in terms of reducing the percentage of patients who suffer from nausea or vomiting during the course of their treatment, if that is what was intended, but they do not. As discussed above, they use broader language, “diminished incidence.” And third, the argument ignores the discussion of the “adaptation” in the Brief Description of the Invention and the implications of that discussion on the construction of “diminished incidences of nausea and emesis.”<sup>8</sup>

### **3. The Prosecution History**

The prosecution history provides no guidance as to the meaning of the phrase “with diminished incidences of nausea and emesis.” That phrase appeared in the method claims filed

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<sup>8</sup> The vacated Markman ruling also indicates that, because the patentees used both the term “incidence” and “level” to refer to nausea, they must have meant to differentiate between the two terms. [Ex. 7 at 18]. But there is nothing in the intrinsic record, including the context in which those terms appear in the specification, to suggest that the patentees intended to distinguish between the two terms.

with Wyeth's first application in the chain [Ex. 10 at WYETH 002-000953], and neither Wyeth nor the examiners commented on the phrase during the prosecution. [Exs. 10-15].

#### **4. Extrinsic Evidence**

Wyeth's construction of the phrase "diminished incidences of nausea and emesis" which embraces both degree and frequency is fully consistent with the ordinary and common dictionary definitions of the words that make up the term. The American Heritage College Dictionary defines "incidence" as the "[e]xtent or frequency of occurrence." [Ex. 17 at 686]. Similarly, Webster's Third New International Dictionary defines "incidence" as "rate, range, or amount of occurrence or influence." [Ex. 18 at 1142]. Likewise, Wyeth's interpretation of "diminished incidences" also is consistent with the definition of "diminish," which, as noted above, Webster's Third New International Dictionary defines as "to make less or cause to appear less: to reduce in size, number, or degree." [Ex. 16 at 634].

In addition, Wyeth's expert in psychiatry and psychopharmacology, Dr. Hollander, agrees that the term "diminished incidence" encompasses not only reduced frequency but also degree (severity, duration, intensity, etc.). [Ex. 19] For example, Dr. Hollander states that "I understand the phrase 'diminished incidence(s) of nausea and emesis' in the context of those patents to encompass the level, extent, degree, amount, range and/or frequency of nausea and vomiting." [Ex. 19 at 5]. He further states:

In my experience with many patients suffering from psychiatric disorders, partial relief of adverse events (such as nausea or vomiting) is quite significant and clinically meaningful and can mean the difference between adherence to treatment with the medicine and noncompliance. In fact, in my opinion, severity and duration of adverse events are the most important factors in achieving a successful long term outcome, such as remission, in the treatment of psychiatric disorders.

[Ex. 19 at 6]. Impax's construction artificially narrows the numerous ways to measure the improvements in nausea and vomiting that result from the patented inventions.

**D. Construction Of “A Method For Eliminating The Troughs And Peaks Of Drug Concentration In A Patient’s Blood Plasma”**

The parties propose somewhat different meanings for the claim phrase “A method for eliminating the troughs and peaks of drug concentration in a patient’s blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride.” Wyeth contends the phrase means:

A method in which the extended release formulation is administered once in a 24-hour period, resulting in a venlafaxine blood plasma concentration that rises to a maximum value, followed by a generally protracted decrease over the remaining period while maintaining during that 24-hour period levels of venlafaxine in blood plasma that are sufficient to provide, during the course of treatment, relief from the condition being treated, thereby eliminating the multiple sharp peaks and troughs resulting from multiple daily dosing of the same total daily dose of the immediate release formulation as reflected in a graph of venlafaxine blood plasma concentration versus time.

Impax contends the phrase means:

the peak(s) and trough(s) due to the “therapeutic metabolism” of any second or third dose given in a single day is eliminated by dosing only once in 24 hours.

The proposed interpretations differ primarily in that Wyeth proposes interpreting the words “peaks and troughs,” and Impax proposes no interpretation for these terms.

**1. The Claim Language**

The claim language appears as the preamble to claims 21, 24, and 25 of the ‘171 patent and claims 2, 5, and 6 of the ‘958 patent. The claims themselves support Wyeth’s proposed construction because each recites a single peak blood plasma level that occurs somewhere between about four and about eight hours after administration. Because this time to peak blood plasma level is extended, the claim language itself supports an interpretation wherein the rise and decline of blood plasma levels of drug are flattened, *i.e.*, less sharp, than the immediate release formulation.

**2. The Patent Specification**

The specification describes the pharmacokinetic properties of the immediate release venlafaxine formulation that led to the need for plural daily dosing as follows:

In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until subtherapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug.

[Ex. 1, col. 1, l. 66 - col. 2, l. 7]. These rapid increases and decreases in blood plasma levels of the drug are the “peaks and troughs” the inventors sought to overcome.

The specification describes “eliminating the troughs and peaks” as follows:

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets.

[Ex. 1, col. 2, ll. 20-28]. This discussion demonstrates that the inventors did not contemplate eliminating peaks and troughs altogether, but rather described their invention as a method for obtaining “a flattened drug plasma concentration to time profile.” The discussion in the patent immediately following the above-quoted excerpt further highlights this point:

In essence, the plasma levels of venlafaxine . . . hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period.

[Ex. 1, col. 2, ll. 28-36]. Thus, the specification equates “eliminating the troughs and peaks of drug concentration in a patient’s blood plasma attending the therapeutic metabolism of plural daily doses of venlafaxine hydrochloride” with a pharmacokinetic profile in which the venlafaxine blood plasma concentration resulting from the extended release formulations “rises to a maximum value, followed by a generally protracted decrease,” maintaining “levels of venlafaxine in blood plasma that are sufficient to provide, during the course of treatment, relief from the condition being treated.” In other words, the claimed extended release formulations replace all of the sharp, multiple peaks and troughs experienced with the plural daily dosing of

the immediate release formulation with a more controlled, flattened blood plasma drug concentration to time profile, which necessarily has a peak followed by a more protracted gradual decline. Wyeth's construction, therefore, merely reflects what the specification says it means to "eliminat[e] the troughs and peaks."

Impax's construction, in contrast, wholly ignores the specification and requires that the peak(s) and trough(s) of only a second or third dose be eliminated, and not the first sharp peak and trough resulting from administration of the first dose of an immediate release venlafaxine product. Such a construction is contrary to the entire gist of the specification and indeed the claims themselves. Likewise, Impax's construction ignores the requirement for therapeutic blood levels maintained over the full twenty-four hour period, and is thus at odds, again, with the specification and the claim language.

### **3. The Prosecution History**

The prosecution history provides no guidance as to the meaning of this phrase. The phrase appeared in the preamble of the original method claim 10 filed with Wyeth's first application in the chain [Ex. 10 at WYETH 002-000953], and neither Wyeth nor the examiners commented on the phrase during the prosecution. [Exs. 10-15].

### **4. Extrinsic Evidence**

Dr. Sawchuk, an expert in the field of pharmacokinetics, has reviewed the intrinsic record, and has concluded that the "method for eliminating the troughs and peaks . . ." language in claims 21, 24 and 25 of the '171 patent and claims 2, 5 and 6 of the '958 patent would be readily apparent to one skilled in the art upon reading various portions of the specification, including the patent abstract, and column 1, line 63 to column 2, line 38 of the '171 patent. [Ex. 20 Sawchuk Decl. at 9]. Dr. Sawchuk states that the phrase refers to a method in which the extended release formulation is given to a patient over the course of treatment once daily, which results in a rise in venlafaxine blood plasma concentration, followed by a generally protracted decrease over the rest of the 24 hour period. [Ex. 20 Sawchuk Decl. at 9]. He notes that this profile replaces the multiple sharp peaks and troughs in venlafaxine plasma concentration when

the same daily dose of the immediate release dosage form of venlafaxine hydrochloride is administered to a patient two or three times daily. [Ex. 20 Sawchuk Decl. at 9]. Furthermore, in Dr. Sawchuk's view, the phrase also means that the blood levels experienced by a patient treated with the once-daily extended release formulation of venlafaxine hydrochloride are therapeutic—that is, sufficient to provide relief from the condition being treated over the course of therapy. [Id.]

Therefore, Wyeth's proffered construction is consistent with both the intrinsic and extrinsic evidence.

## V. CONCLUSION

For the reasons discussed above, Wyeth submits that its constructions of the three claim terms at issue are fully supported by both the intrinsic and extrinsic evidence. Wyeth respectfully requests that the Court adopt Wyeth's construction of these terms.

Respectfully submitted,

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**CERTIFICATE OF SERVICE**

I, Karen Jacobs, hereby certify that on May 14, 2007, I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filings(s) to the following:

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